Apixaban for treatment of venous thromboembolism associated with cancer

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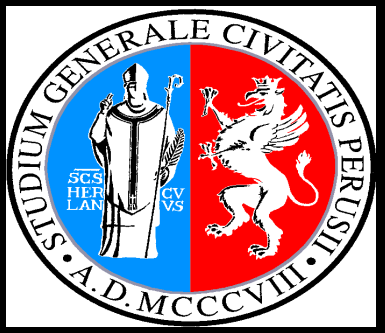


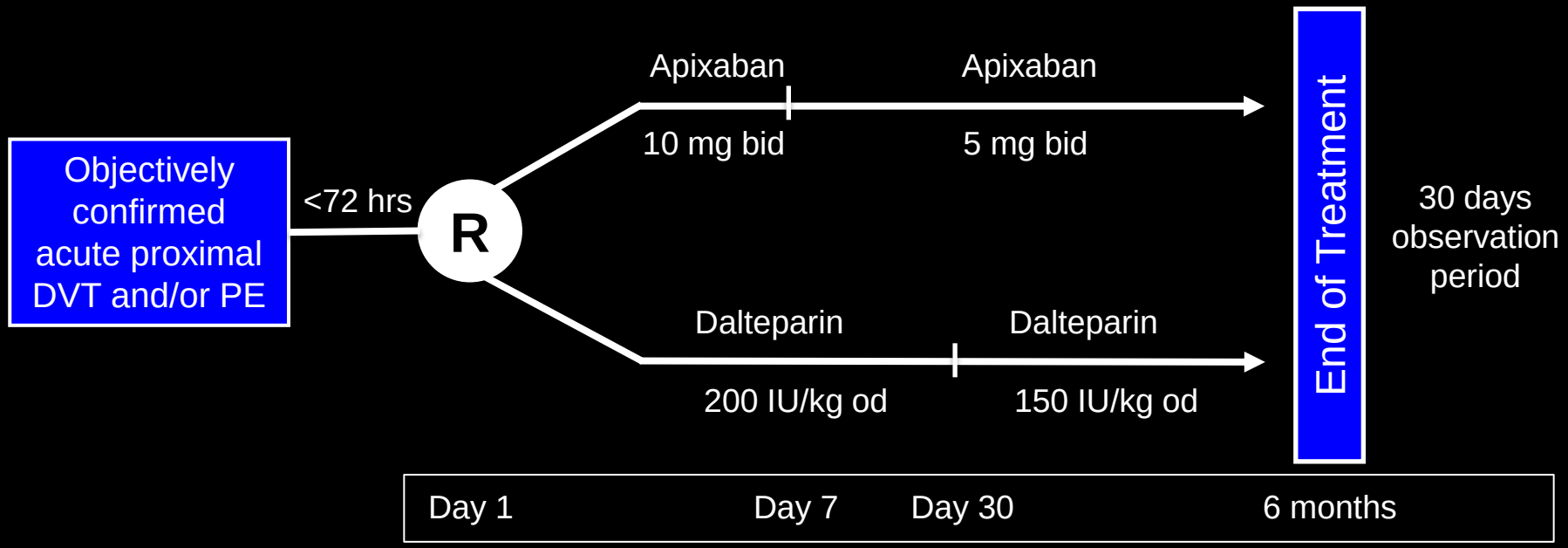
Study background

- The high risk of recurrent venous thromboembolism and bleeding in patients with cancer requires specific studies on anticoagulant treatment
- Major guidelines recommend low-molecular-weight heparin and have recently added edoxaban and rivaroxaban
- The clinical benefit of these oral agents is limited by the high risk of bleeding, mainly occurring at gastrointestinal sites

The Caravaggio study

Aim: To assess whether oral apixaban was non-inferior to subcutaneous dalteparin for the treatment of proximal DVT and/or PE in patients with cancer

Design: Randomized, open-label, PROBE, non-inferiority study



Investigator-Initiated Study supported by an unrestricted grant from the Bristol-Myers Squibb/Pfizer Alliance

Inclusion criteria (I)

Consecutive patients with cancer and objectively confirmed:

- symptomatic or incidental*, proximal lower-limb DVT or
- symptomatic pulmonary embolism or
- incidental* pulmonary embolism in a segmental or more proximal pulmonary artery

* Incidental DVT or PE were events detected on imaging tests performed for reasons other than clinical suspicion of venous thromboembolism. The maximum proportion of patients entering the study with incidental VTE was set at 20% of the overall study population

Inclusion criteria (II)

Any type of cancer other than basal-cell or squamous-cell carcinoma of the skin, primary brain tumor or known cerebral metastases and acute leukemia

- Active cancer

  defined as diagnosis of cancer within six months before the study inclusion, or receiving treatment for cancer at the time of inclusion or during 6 months prior to randomization, or recurrent locally advanced or metastatic cancer

- History of cancer*

  Cancer diagnosed within 2 years before the study inclusion

* The maximum proportion of patients entering the study with history of cancer was set at 20% of the overall study population

Main exclusion criteria

- Age lower than 18 years
- ECOG Performance Status III or IV
- Life expectancy of less than 6 months
- Therapeutic doses of LMWH, fondaparinux, UFH or VKA for >72 hours before randomization
- Indication for anticoagulant treatment for a disease other than the index VTE
- Concomitant use of strong inhibitors or inducers of both CYP-3A4 and P-gp
- Concomitant thienopyridine therapy (clopidogrel, prasugrel, or ticagrelor) or aspirin over 165 mg daily or dual antiplatelet therapy
- Active bleeding or a high risk of bleeding contraindicating anticoagulant treatment
- Hb < 8 g/dL or platelet count < $75x10^9$/L or creatinine clearance < 30 ml /min)

Study outcomes

Efficacy:

Objectively confirmed recurrent proximal DVT or PE occurring during the study treatment period:

- proximal DVT of the lower limbs (symptomatic or incidental)
- DVT of the upper limbs (symptomatic)
- pulmonary embolism (symptomatic or incidental)

Safety:

Major bleeding (EMA definition*)

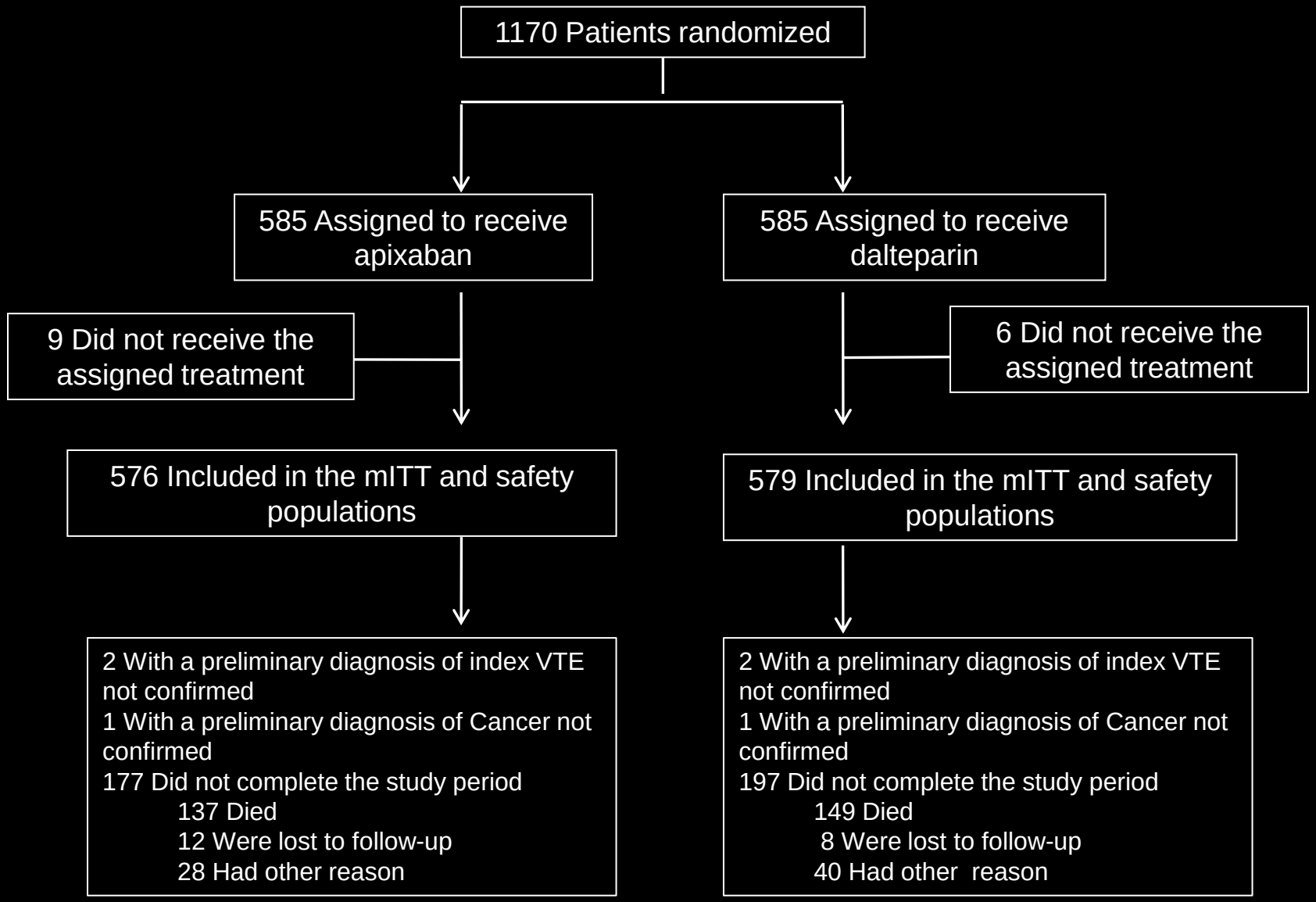
* EMA definition: ISTH criteria (acute clinically overt bleeding with ≥ 1 of the following: decrease in hemoglobin ≥ 2 g/dl; transfusion ≥ 2 units of packed red blood cells, occurring in at least one of the following critical sites: intracranial, intra-spinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome or retroperitoneal; fatal) and bleeding that necessitates acute surgical intervention

Study hypothesis: statistics and analysis

- Hypothesis: apixaban non-inferior to conventional therapy for primary efficacy outcome (VTE recurrence)
- Estimated rate of VTE with dalteparin: 7% at 6 months
- Hazard rate non-inferiority margin of 2.00
- 80% power, at a one-sided alpha level of 0.025
- Sample size: 1168 patients
- Drop-out rate of 20% lost in total patient-years
- Primary analysis population: modified intention-to-treat (m-ITT)

This estimate is consistent with a drop-out rate of 40% assuming patients discontinued uniformly during the follow-up (mean discontinuation time equal to 3 months)

Patient disposition



Patient characteristics at baseline

	Apixaban N=576	Dalteparin N=579
Mean age, y (SD)	67.2 (11.3)	67.2 (10.9)
Male sex, n (%)	292 (50.7)	276 (47.7)
Mean weight, kg (SD)	75.7 (16.1)	76.1 (16.7)
PE with or without DVT	304 (52.8)	334 (57.7)
DVT only	272 (47.2)	245 (42.3)
Symptomatic DVT or PE	460 (79.9)	465 (80.3)
Incidental DVT or PE *	116 (20.1)	114 (19.7)
Active cancer, n (%)	559 (97.0)	565 (97.6)
Recurrent Locally Advanced or Metastatic cancer, n (%)	389 (67.5)	396 (68.4)
Treatment for cancer at the time of inclusion, n (%) §	350 (60.8)	367 (63.4)
Treatment for cancer within previous 6 months, n (%) §	143 (24.8)	129 (22.3)
Treatment for cancer during the study period, n (%) §	344 (59.7)	346 (59.8)
Previous venous thromboembolism, n (%)	45 (7.8)	61 (10.5)
Platelet count < 100,000 per mm^3, n (%)	21 (3.6)	22 (3.8)
Creatinine clearance ≤50 ml/min, n (%)	51 (8.9)	61 (10.5)

§ Cancer treatment includes anticancer drug therapy (cytotoxic, hormonal, targeted or immunomodulatory), radiotherapy, surgery, or a combination of these therapies

Type of cancer

	Apixaban N=576	Dalteparin N=579
Solid tumor, n(%)	543 (94.3)	527 (91.0)
Colorectal	121 (21.0)	113 (19.5)
Lung	105 (18.2)	95 (16.4)
Breast	79 (13.7)	76 (13.1)
Genitourinary	66 (11.5)	73 (12.6)
Gynecological	60 (10.4)	59 (10.2)
Pancreatic or hepatobiliary	44 (7.6)	43 (7.4)
Upper gastrointestinal	23 (4.0)	31 (5.4)
Head and Neck	14 (2.4)	8 (1.4)
Bone/soft tissue	11 (1.9)	7 (1.2)
Skin-melanoma	4 (0.7)	7 (1.2)
Other	16 (2.8)	15 (2.6)
Hematological malignancy, n (%)	33 (5.7)	52 (9.0)

Primary efficacy outcomes

	Apixaban N=576	Dalteparin N=579	Hazard Ratio (95% CI)	P Value
Recurrent VTE, n (%)	32 (5.6)	46 (7.9)	0.63 (0.37–1.07)	<0.001 for noninferiority 0.08 for superiority
Recurrent DVT, n (%)	13 (2.3)	15 (2.6)	0.87 (0.34–2.21)	
Recurrent PE, n (%)	19 (3.3)	32 (5.5)	0.54 (0.29–1.03)	
Fatal PE, n (%)	4 (0.7)	3 (0.5)	1.93 (0.40–9.41)	

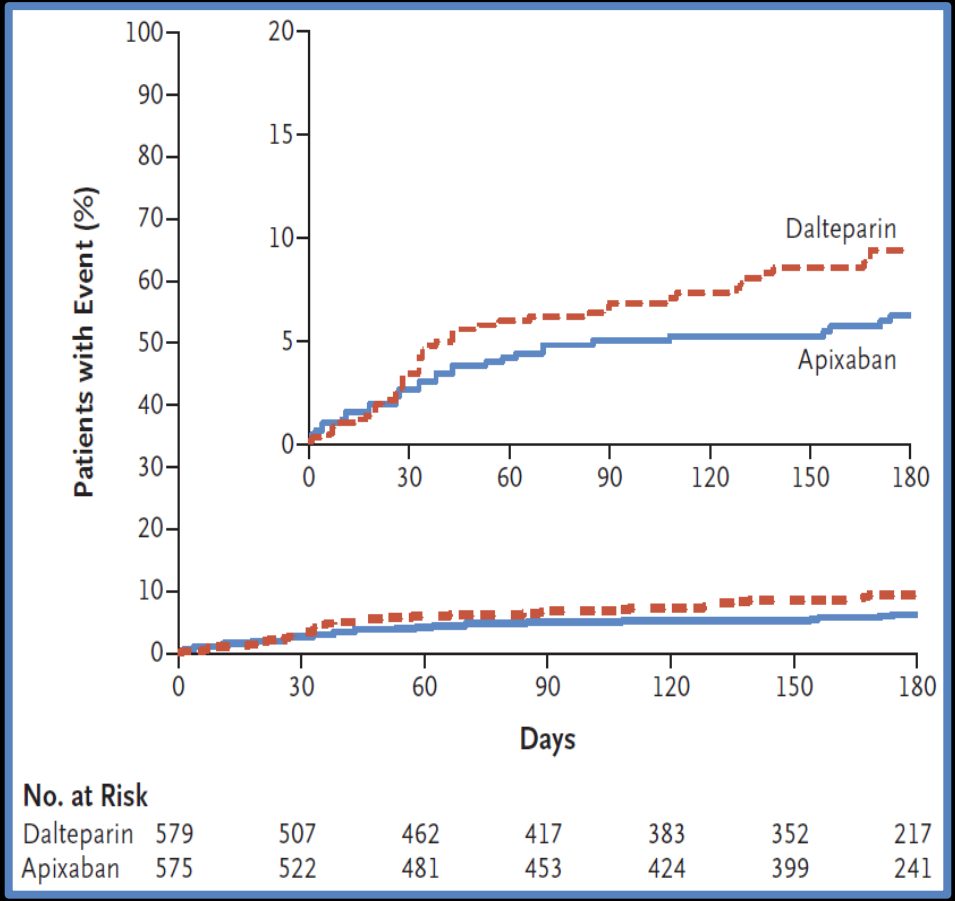
Primary and secondary safety outcomes

	Apixaban N=576	Dalteparin N=579	Hazard Ratio (95% CI)	P Value
Major Bleeding, n (%)	22 (3.8)	23 (4.0)	0.82 (0.40–1.69)	0.60
Major GI bleeding, n (%)	11 (1.9)	10 (1.7)	1.05 (0.44–2.50)	
Major non GI bleeding, n (%)	11 (1.9)	13 (2.2)	0.68 (0.21–2.20)	
CRNMB, n (%)	52 (9.0)	35 (6.0)	1.42 (0.88-2.30)	
MB & CRNMB, n (%)	70 (12.2)	56 (9.7)	1.16 (0.77-1.75)	

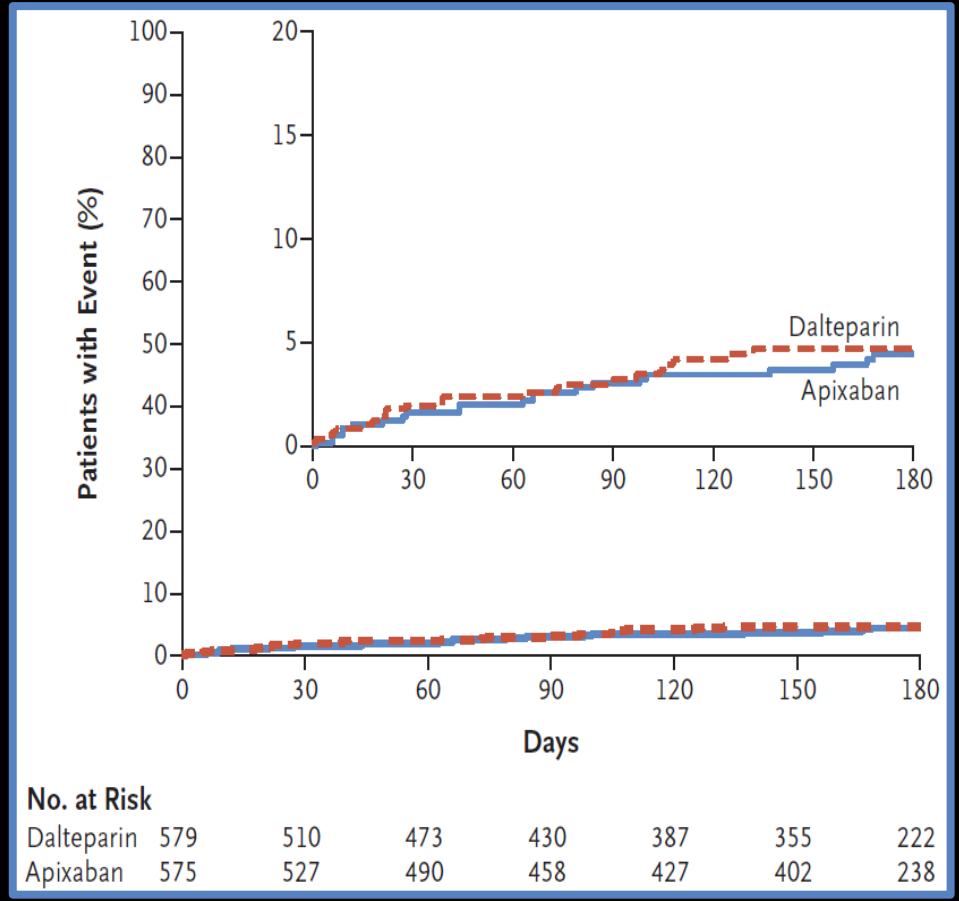
CRNMB, clinically relevant nonmajor bleeding

Cumulative event rate of VTE recurrences and major bleeding

Recurrent VTE



Major Bleeding



Conclusions

Oral apixaban was noninferior to subcutaneous dalteparin for the treatment of cancer-associated venous thromboembolism

No increase in the risk of major bleeding was observed in particular at the gastrointestinal sites.

Findings of Caravaggio expand the proportion of patients with cancer-associated thrombosis who are eligible for treatment with the oral direct anticoagulants, including patients with gastrointestinal cancer

Study Committees

Steering Committee	Data Monitoring Committee	Central Adjudication Committee
Giancarlo Agnelli, Cecilia Becattini, Guy Meyer, Andres Muñoz, Menno V. Huisman, Jean Marie Connors, Alexander Cohen, Rupert Bauersachs, Benjamin Brenner, Adam Torbicki, Maria Rosales Sueiro, Catherine Lambert, Gualberto Gussoni, Mauro Campanini, Andrea Fontanella, Giorgio Vescovo, Melina Verso	Henri Bounameaux, Sabine Eichinger, Claudio Cimminiello	Walter Ageno, Michele Duranti, Francesco Guercini, David Jimenez Castro, Sonia Fatigoni, Arnaud Perrier, Marco Moia

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